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Family's Debate Mirrored Scientists' on Gene Therapy Risk

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Just before Paul Gelsinger sent his son off to Philadelphia to take part in a gene therapy experiment for the teenager's childhood disease, the Tucson man had a heated dining room debate with his mother-in-law over the wisdom of the trip.

He's healthy, she argued. He's doing well on his current treatment. Why take the gamble?

It's a low-risk study, Gelsinger told her. He wants to do it. And it might lead to a cure for the rare genetic ailment he had, called ornithine transcarbamylase deficiency.

"Turns out she was right," the devastated father said yesterday.

Gelsinger's son died shortly after starting the pioneering treatment at the University of Pennsylvania in Philadelphia--the first apparent casualty since scientists began experimenting with ways to permanently alter disease-causing genes. The death is being investigated by the university and federal officials.

Although he didn't know it at the time, Gelsinger's argument with his mother-in-law was a dinner table replay of a similarly vigorous discussion over a meeting room table four years ago, when a federal advisory committee wrestled with whether to endorse the controversial study.

Of particular concern to committee members was the researchers' decision to experiment on patients who were doing well on conventional treatment or no treatment at all. The first round of human testing for new therapies is usually done on ill patients who haven't responded to standard treatments, and thus have less to lose by trying unproven approaches.

The Pennsylvania protocol was discussed at length at that December 1995 meeting of the Recombinant DNA Advisory Committee (RAC), an advisory group to the director of the National Institutes of Health that examines the scientific and ethical basis of all proposed gene therapy experiments involving federal funds.

Robert P. Erickson, an RAC member affiliated with the University of Arizona, opened the discussion with several criticisms of the proposed experiment. The study was not justified, he said, in part because the procedure was very "invasive"--a catheter would have to be threaded through critical blood vessels and the new genes would be delivered directly into the liver via millions of living viruses that had the potential to trigger organ damage--and because most of the patients to be studied were in good health and many in fact had never experienced symptoms.

At a minimum, he suggested, the viruses should be delivered through a less dangerous intravenous line. The Philadelphia researchers, in attendance at the meeting, accepted that advice. But ultimately they used the original approach anyway because of fears that the intravenous approach might create problems of its own by delivering the new genes to the wrong parts of the body.

That reversal was approved in private meetings with the Food and Drug Administration, but was never reviewed in public by the RAC--a fact that concerned some committee members, who did not learn about the change until they read it in newspapers yesterday.

"The public and the RAC didn't know," said LeRoy B. Walters, a Georgetown University ethicist who sat on the committee. "I think the early years of a promising area like gene therapy ought to be out in the light of day."

Researchers said on Tuesday that the method of delivery is one of several possible reasons that Jesse Gelsinger went into multiple organ failure soon after getting his first infusion of new genes--although none of the previous 17 patients had suffered any ill effects from the treatment.

At the 1995 meeting, Erickson also said he was troubled by the fact that the treatment did not have the potential to lead to a long-term improvement, since a single infusion of viruses would not be curative and subsequent infusions would be neutralized by the body's immune response.

Another committee member, Rochelle Hirschhorn, expressed similar reservations. It would be more promising to pursue further work in laboratory animals, she said, and then use those results to help design a safer approach before starting work in people.

Study leaders James Wilson and Mark Batshaw spent considerable time explaining why they thought the project was worthy and ultimately prevailed. The RAC approved the project, with some modifications to satisfy members' concerns, 12 to 1 (with four abstentions), with Erickson the sole dissenter.

There is an irony to Erickson's leading role in the debate over the Pennsylvania study. It was a close colleague of his at the University of Arizona whom Jesse Gelsinger approached for advice on what to do about his disease. That colleague, Randy Heidenreich, who

specializes in metabolic diseases like the one the boy had, recommended that Gelsinger look into the Philadelphia experiment. Erickson's office is just two doors away from Heidenreich's. But the boy and his father never spoke to Erickson about the study.

Paul Gelsinger said yesterday he had no idea that there had ever been a big debate about the study. But he said he has faith that the renewed soul-searching by scientists will lead to some good.